REMARKS

At the outset, Applicants submit that a Revocation and New Power of Attorney to the undersigned attorney was submitted in this application on July 2, 2007. Please address future correspondence to the undersigned attorney.

Following entry of the present amendment, claims 33, 35, and 36 remain in the application for consideration. Claims 1-32, 34, 37-66 were previously cancelled without prejudice.

Rejections under 35 USC §112, First Paragraph

Claims 33 and 35-36 were rejected as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

To address the rejection, Applicants herein amend claim 33 to recite that the incubation mixture comprises, among other things, a sequence of SEQ ID NO: 2; and an isolated protein comprising the amino acid of SEQ ID NO:4 with an altered PYI motif at residues 564-566 or a fragment thereof comprising SEQ ID NO:5 or SEQ ID NO:6. Applicants now submit that this rejection is overcome.

Claims 33 and 35-36 were rejected as allegedly failing to comply with the enablement requirement, and that "undue" experimentation is required to practice the method of the

claimed invention. Applicants respectfully traverse the rejection.

Claim 33 recites a negative control assay for testing a substance that has shown to bind to a normal HIF protein. In this control assay a HIF protein comprising an altered PYI motif at residues 564-566 is substituted for a normal HIF protein. Claim 33 specifically recites very specific steps:

33. A method of screening for an agent which modulates the function of a protein comprising the amino acid sequence of SEQ ID NO:5, comprising

incubating a mixture comprising:

an isolated protein comprising the amino acid of SEQ ID NO:4 with an altered PYI motif at residues 564-566 or a fragment thereof comprising SEQ ID NO:5 or SEQ ID NO:6;

the sequence of SEQ ID NO:2; and

a candidate agent under conditions whereby, but for the presence of said agent, said isolated protein mediates VHL-dependent degradation or physically interacts with VHL at a reference affinity;

detecting the binding affinity of said isolated protein to SEQ ID NO:2 to determine an agent-biased affinity;

wherein a difference between said reference affinity and said agent-biased affinity indicates that said agent modulates the functional activity of said isolated protein to said sequence of SEQ ID NO:2.

Thus, in its most basic form, the claimed invention is an assay comprising an incubating step and a detecting step. The assay comprises mixing HIF or a fragment of HIF comprising the normal PYI motif with test substances that can hamper the interaction between the HIF and the VHL protein or a fragment thereof. The HIF protein would not be degraded in the presence of such a hampering test substance. The modified PYI motif according to the present invention brings about a lower affinity between the HIF protein and VHL. Consequently, the HIF protein is degraded by VHL to a less degree compared to the native sequence.

It is of interest to identify a substance that specifically hampers the PYI mediated interaction between HIF and VHL and therefore, the control assay would then comprise mixing HIF or a fragment of HIF comprising the altered PYI motif with test substances that can hamper the interaction between the HIF and the VHL protein. The test substances would then not hamper the low affinity interaction between HIF (PYI-defective) and VHL or further promote the degradation of the HIF protein with the altered PYI motif.

Applicants submit that there is sufficient disclosure in the specification to teach one of skill in the art to practice the invention. In particular, the extensive description,

Figures, and Examples 1-10 all describe in detail use the invention such that one of skill in the art could practice it. Applicants therefore submit that undue experimentation is not required to practice the invention, and that this rejection is overcome..

In addition, the Examiner cites Cockman et al., J. Biol. Chem. 275:25733-25741, published on 18 August 2000, and Tanimoto et al., EMBO J. 19:4298-4309, published on 15 August 2000, as evidence of the prior art. Applicants submit that these technical journal articles were both published after the priority date of the present application (August 7, 2000), and therefore these articles cannot be considered prior art.

Applicants submit that the claims are now in condition for allowance, and a Notice of Allowance is eagerly solicited.

Any fees due with this request may be charged to Deposit Account 23-1665, Customer Number 27267.

If the Examiner has any questions or feels that a discussion with Applicants' representative would expedite prosecution, the Examiner is invited and encouraged to contact Applicants' undersigned representative at the telephone number listed below.

Respectfully submitted,

LORENZ POELLINGER ET AL.

By Todd E. Garabedian

Todd E. Garabedian, Ph.D.
Registration No. 39,197
Attorney for Applicants

WIGGIN AND DANA LLP
One Century Tower
New Haven, CT 06508

Telephone: (203) 498-4400
Fax: (203) 782-2889

Date: 21 DEC 2007

\18516\6\57958.1